REMARKS

Claims 7, 9, 10, and 18 to 20 are pending in this application. Applicants have amended claim 7. Support for this amendment can be found in the specification, for example, at page 1, lines 24-27.

Applicants respectfully point out that the Information Disclosure Statement filed on October 1, 2004 has yet to be considered and initialed by the Examiner. Applicants request that the Examiner review the references listed on form PTO-1449, initial and date each reference, and send applicants a copy of the executed form.

Examiner Interview

Applicants thank Examiners Ford and Minnifield for the telephonic interview of November 4, 2005 in which the subject matter of the pending claims and the obviousness rejection of the claims were discussed.

Withdrawn Rejections

The Office Action at page 2 states that the rejection of claim 18 under 35 U.S.C. § 103(a) has been withdrawn. Applicants seek clarification on this withdrawn rejection, because the maintained § 103(a) rejection lists claim 18. Applicants assume that the rejection of claim 18 under 35 U.S.C. § 112, second paragraph has been withdrawn because this rejection has not been reiterated from the previous Office Action, but request that the Office clarify this issue.

Subject Matter of the Claims

The subject matter recited in the claims is directed to compositions that include a carrier group covalently coupled to one or more isolated oligosaccharides that are cleaved from, or are chemically synthesized to correspond to oligosaccharides that are cleaved from, a chlamydial glycolipid exoantigen (GLXA). As discussed in the telephonic interview of November 4, 2005, an oligosaccharide is a chain of sugars. All glycolipids, including GLXA, are made up of two

types of molecules: lipids and oligosaccharides. The oligosaccharides recited in the claims are isolated, meaning that they are not part of the glycolipid, i.e., the claimed oligosaccharides contain only the sugars, and not the lipids of the glycolipid. Applicants have amended claim 7 to more clearly indicate that the oligosaccharides are not part of the complete GLXA, but rather, are cleaved from, or are chemically synthesized to correspond to oligosaccharides cleaved from, a GLXA.

35 U.S.C. § 103(a)

Legal Standards for an Obviousness Rejection

The Office Action states on page 7, "There is nothing on the record to show that the combination of teachings would not suggest the claimed invention." The statement is reiterated, with respect to the two § 103(a) rejections of claim 10, on pages 9 and 12 of the Office Action. Applicants respectfully submit that the Office has inadvertently used the incorrect legal standard in maintaining its obviousness rejection, and has improperly shifted the burden of proof onto applicants.

As the Examiner is no doubt aware, the correct legal standard that governs an obviousness rejection under 35 U.S.C. § 103(a) requires the Patent and Trademark Office ("PTO") to make out the *prima facie* case of obviousness before the burden can shift to the applicant to rebut such a case. "The PTO has the burden under section 103 to establish a *prima facie* case of obviousness" (*In re Fine*, 837 F.2d 1071 (1988)). Applicants submit that the Office has incorrectly placed the burden to the applicant to disprove an element of the *prima facie* case that the Office Action is required to, yet has failed to, establish.

As stated in MPEP § 2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

All three elements of the *prima facie* case must be established by the Office Action. If even one element is lacking, a *prima facie* case of obviousness has not been established. Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of obviousness with respect to the instant application, because none of the elements of a *prima facie* case has been established with respect to claim 7 and the claims that depend therefrom.

35 U.S.C. § 103(a): Claim 7 to 9 and 18 to 20

Applicants thank Examiner Ford for the telephone discussion of August 15, 2005 in which the Examiner clarified which pages of the Whittum-Hudson reference (*Nature Medicine* **2**:1116-1121 (1996)) were meant to be cited in the Office Action. According to Examiner Ford, on page 5 of the Office Action, each of the three cites to Whittum-Hudson (cited pages were listed as page 4063, 4062, and 4062, respectively) should cite page 1116, while the first cite to Whittum-Hudson on page 6 of the Office Action (listed page was 4068) should cite page 1116, and the second cite (listed as page 4062) should cite page 1117.[1]

Claims 7 to 9, and 18 to 20 have been rejected as allegedly obvious over Whittum-Hudson et al. (*Nature Medicine* **2**:1116-1121 (1996)) in view of Dick Jr. et al. (*Conjugate Vaccine, Contrib. Microbiol. Immunol.* **10**:48-114 (1989)). Applicants respectfully submit that a *prima facie* case of obviousness has not been made against these claims.

The Prior Art Fails to Teach or Suggest All the Claim Limitations

The claims are directed to compositions that include a carrier group covalently coupled to one or more isolated oligosaccharides that are cleaved from, or are chemically synthesized to correspond to oligosaccharides cleaved from, a GLXA. Applicants respectfully submit that neither Whittum-Hudson nor Dick Jr. teaches or suggests all of the elements recited in the claims, specifically, neither reference, alone or in combination, teaches or suggests one or more GLXA oligosaccharides.

[1] Applicants point out that the page numbers listed in the Office Action correspond to another article by Whittum-Hudson et al., *Vaccine*, 19:4061-4071 (2001), and that the publication date of this article is after the priority date of the present application. Thus, this paper is not prior art. Further, applicants will demonstrate below that this article also fails to describe the claimed invention.

Whittum-Hudson describes the production of GLXA anti-idiotypic antibodies and their use as a vaccine to protect against *C. trachomatis* infections. An intact GLXA, containing both the oligosaccharide and lipid components, was used to produce such antibodies (see, e.g., Whittum-Hudson at page 1117, second column). Whittum-Hudson does not describe, or even suggest, an isolated oligosaccharide without the lipid component, i.e., GLXA oligosaccharides. Nowhere does Whittum-Hudson teach or suggest that useful oligosaccharides should, or could, be isolated from GLXA, or that such isolated oligosaccharides should (or could) be coupled to a carrier group.

The Office Action alleges, "[i]t should be noted that Whittum-Hudson et al disclose the generation of the same GLXA oligosaccharide as that disclosed in the instant application (see page 4063 [1116] or the prior art and pages 14-15 of the instant application)" (Office Action at page 5). Applicants respectfully disagree. On page 1116, Whittum-Hudson states, "[t]he antigenic determinant(s) of GLXA resides on its polysaccharide component ..." Whittum-Hudson may have identified where on intact GLXA an antigenic determinant resides. However, this reference does not teach or suggest that one or more oligosaccharides should (or could) be isolated, e.g., cleaved from, or chemically synthesized to correspond to oligosaccharides cleaved from, GLXA. This quoted passage also does not teach or suggest that one or more isolated oligosaccharides should (or could) be covalently coupled to a carrier group.

The protocol on page 14-15 of the present application describes a way to obtain intact GLXA itself. Page 15, lines 28-31, goes on to describe how to isolate one or more oligosaccharides from the intact GLXA. As described on page 15: "the glycolipid was subjected to mild trifluoroacetolysis ..." The protocol on page 7, lines 1-4, of the present application also describes how to prepare one or more isolated oligosaccharides after intact chlamydial GLXA has been isolated: "oligosaccharides can be released from an isolated glycolipid. This can be done using, e.g., standard mild acid hydrolysis or glycosidase treatment." As demonstrated by these examples, the preparation of one or more isolated oligosaccharides requires an additional step after intact GLXA has been obtained.

In contrast, Whittum-Hudson only describes using, not isolating, intact GLXA (with its complete lipid and polysaccharide components) on page 1118. In fact, not only does this reference fail to describe the isolation of an oligosaccharide from a glycolipid, this reference does not even describe or suggest the isolation of intact GLXA itself. Page 1116 of Whittum-Hudson, which the Office Action uses to support its allegation that this reference describes an isolated intact GLXA, does not describe the isolation of either an oligosaccharide or of intact GLXA. This page merely states that the antigenic determinant of GLXA resides on its polysaccharide component. This reference fails to teach or suggest the one or more isolated GLXA oligosaccharides that are recited in the claims. Likewise, page 4063 of the *Vaccine*, 19:4061-4071 (2001) article, which was **published after applicants' priority date**, also does not describe the one or more isolated oligosaccharides recited in the claims. Section 2.4 on page 4063 of this article describes only how to obtain intact GLXA. It does not describe the additional step needed to isolate one or more oligosaccharides from GLXA. Thus, neither of the Whittum-Hudson references teaches or suggests the one or more isolated oligosaccharides recited in claim 7, or that such isolated oligosaccharides should (or could) be coupled to a carrier group.

Dick Jr. describes certain glycoconjugate vaccines, e.g., vaccines that use carbohydrate antigens, such as oligosaccharides, from capsular polysaccharides (CPS) and lipopolysaccharides (LPS) (pages 58-60). However, Dick Jr. does not describe GLXA or that one or more oligosaccharides could be cleaved from (or chemically synthesized based upon) GLXA, much less that such oligosaccharides should (or could) be covalently coupled to a carrier group.

Because the combined references fail to teach or suggest the one or more isolated GLXA oligosaccharides, applicants submit that a *prima facie* case of obviousness has not been established and request that the obviousness rejection of 7 to 9 and 18 to 20 be withdrawn.

A Suggestion or Motivation to Combine the References is Lacking

The Office Action alleges on pages 5-6 that:

> One of ordinary skill in the art would be motivated to couple an GLXA oligosaccharide to a carrier because Dick, Jr. et al teach that carbohydrate

components can be covalently linked to carrier proteins thereby demonstrating a thymus dependent (TD) response to carbohydrate components and enhancing the immune response to carbohydrate component.

Dick Jr. describes the conjugation of several types of bacterial carbohydrate components, for example, Dick Jr. describes carbohydrate antigens from capsular polysaccharides (CPS) (pages 58-59) and lipopolysaccharides (LPS) (page 60). However, Dick Jr. fails to even mention exoantigens, much less chlamydial GLXA. Next, Dick Jr. lists numerous pathogenic bacterial species for which an improved vaccine is needed: *Haemophilus influenzae, Neisseriae meningitidis, Streptococcus pneumoniae, Salmonella typhi, Pseudomonas aeruginosa, Cryptococcus neoformans, Escherichia coli, Klebsiella, and Vibrio cholerae* (page 48). However, Dick Jr. does not teach or suggest the bacterial genus of the present application, *Chlamydia*. In addition, the Office Action has not presented evidence that the one or more GLXA oligosaccharides recited in claim 7 are sufficiently similar in structure to the oligosaccharides from the bacteria listed in Dick Jr. so as to render the GLXA oligosaccharides recited in claim 7 obvious.

Applicants respectfully submit that a motivation to combine Dick Jr. and Whittum-Hudson would not have existed. Whittum-Hudson describes the success of using anti-idiotypic antibodies to generate protective immunity (see e.g., Abstract at page 1116). Whittum-Hudson demonstrates (on page 1118) that when mice were immunized with either a soluble anti-idiotype antibody (mAb_2) or with intact GLXA, only the mAb_2 was protective against subsequent chlamydial challenge: "Significant reductions in infectious yields were observed [after immunization with mAb_2] even after a >2 log higher challenge dosage, whereas *GLXA in alumina was not protective*" (emphasis added). Because Whittum-Hudson describes that whole GLXA was not protective, no skilled practitioner would have been motivated to isolate one or more oligosaccharides from GLXA and to couple the one or more oligosaccharides to a carrier group, nor would the skilled practitioner have had any reasonable expectation that the resulting composition would have any effect. Further, Whittum-Hudson would have discouraged a skilled practitioner from using isolated oligosaccharides to make vaccines, because this reference

demonstrates that a successful alternative exists, i.e., the use of anti-idiotypic antibodies as vaccines.

Thus, applicants respectfully request that the obviousness rejection of claims 7 to 9 and 18 to 20 be withdrawn, because there would have been no motivation to combine the cited references, and Whittum-Hudson actually teaches away from the combination.

The Combined References Fail to Provide a Reasonable Expectation of Success

Whittum-Hudson states that intact GLXA did not elicit a protective immune response to subsequent challenge (page 1118). Applicants submit that because Whittum-Hudson states that intact GLXA did not work, it could not have motivated a skilled practitioner to isolate oligosaccharides from this glycolipid, couple such oligosaccharides to a carrier group, and expect, not to mention reasonably expect, such a composition to elicit a protective immune response. If the intact GLXA was not protective, why would a skilled practitioner expect an isolated portion (i.e., the oligosaccharide) of GLXA to be protective?

Dick Jr. also fails to provide a reasonable expectation of success. Dick Jr. lists numerous bacterial species from which carbohydrates can be conjugated to a carrier, but this reference is devoid of any mention of any species of *Chlamydia*. If the reference does not mention *Chlamydia*, it cannot provide an expectation of success, not to mention a reasonable expectation of success, that isolating one or more oligosaccharides from a chlamydial exoantigen and conjugating the isolated oligosaccharides to a carrier group would result in a composition that is able to elicit a protective immune response.

If neither reference mentions or suggests one or more isolated GLXA oligosaccharides, and one of the references actually teaches that intact GLXA is not protective, it is not possible for the combination of these references to provide a reasonable expectation of success in making a composition that contains one or more of these isolated GLXA oligosaccharides, and that are covalently coupled to a carrier group. Because the combined references fail to provide a reasonable expectation of success, applicants submit that a *prima facie* case of obviousness has

not been established and request that the obviousness rejection of claims 7 to 9 and 18 to 20 be withdrawn.

35 U.S.C. § 103(a): Claim 10

Claim 10 was rejected as allegedly obvious over Whittum-Hudson and Dick Jr. in view of Semprevivo (*Carbohydrate Research* **177**:222-227 (1988)); or in the alternative, as allegedly obvious over Whittum-Hudson and Dick Jr. in view of Smith (*J. Biol. Chem.* **255**:55-59 (1980)).

First, claim 10 depends from claim 7, and is therefore patentable for the reasons articulated above. Furthermore, applicants respectfully submit that neither Semprevivo nor Smith make up for the deficiencies of Whittum-Hudson and Dick Jr., which are discussed above, and thus the combination of references fails to establish a *prima facie* case of obviousness with respect to claim 10.

The Prior Art Fails to Teach or Suggest All the Claim Limitations

Neither Semprevivo nor Smith describes or suggests one or more isolated GLXA oligosaccharides. Semprevivo describes a method for derivatizing oligosaccharides from the eukaryotic organism *Leishmania mexicana amazonensis*, and indicates that similar methods have been utilized for other eukaryotic organisms, such as *Leishmania tropica*, *Leishmania donovani*, *Trichomonas vaginalis*, *Schistosoma mansoni*, and *Nematospiroides dubius*. Smith describes a method for derivatizing free sialylated oligosaccharides from human milk. Both references fail to teach or even suggest that one or more GLXA oligosaccharides should be isolated or that such oligosaccharides should (or could) be coupled to a carrier group. Because the combined references fail to teach or suggest all of the elements recited in the claims, applicants submit that a *prima facie* case of obviousness has not been established and request that the obviousness rejection of claim 10 be withdrawn.

A Suggestion or Motivation to Combine the References and a Reasonable Expectation of Success Are Lacking

Neither Semprevivo nor Smith make up for the lack of a motivation to combine the references or for the lack of a reasonable expectation of success in Whittum-Hudson and Dick Jr., discussed above.

Semprevivo describes only the conjugation of oligosaccharides from eukaryotic organisms. In reading Semprevivo, alone or in combination with Whittum-Hudson and Dick Jr., a skilled practitioner would not have been motivated to prepare the composition recited in the claims, because none of these references describes or suggests isolated chlamydial oligosaccharides. If none of the references describes or suggests such isolated chlamydial GLXA oligosaccharides, then it would not have been possible for these references to motivate a skilled practitioner to isolate such oligosaccharides or to covalently couple such oligosaccharides to a carrier group. In addition, and importantly, because Whittum-Hudson taught that intact GLXA was not protective, a skilled practitioner would not have expected that an isolated portion (i.e., one or more oligosaccharides) of GLXA could be protective, and thus the combined references also fail to provide a reasonable expectation of success.

Smith describes the use of sialylated human milk oligosaccharides to generate antibodies. In reading Smith, alone or in combination with Whittum-Hudson and Dick Jr., a skilled practitioner would not have been motivated to prepare the composition recited in the claims. Not one of these references teaches or suggests using the methodology used to conjugate sialylated human milk oligosaccharides to conjugate one or more isolated chlamydial GLXA oligosaccharides to a carrier group. If none of the references describes or even suggests the isolated GLXA oligosaccharides recited in the claims, then it would not have been possible for these references to motivate a skilled practitioner to isolate such oligosaccharides or to covalently couple such oligosaccharides to a carrier group. In addition, because Whittum-Hudson taught that intact GLXA was not protective, a skilled practitioner would not have expected that an isolated portion (i.e., the oligosaccharide) of GLXA could be protective, thus, the combined references also fail to provide a reasonable expectation of success.

Because the combined references fail to provide a motivation to combine the references and/or a reasonable expectation of success, applicants submit that a *prima facie* case of obviousness has not been established and request that the obviousness rejection of claim 10 be withdrawn.

CONCLUSION

Applicants respectfully request that the rejections to the claims be withdrawn and that all claims be allowed. No fees are believed due. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 08952-008001.

Respectfully submitted,

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